Gastrointestinal Sarcomas

Analysis of Prognostic Factors

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Clinical and pathologic data from 51 patients with primary sarcomas of the gastrointestinal tract treated from 1951 through 1984 were reviewed to determine clinical presentation, histologic features, treatment, and prognostic factors. The most common signs and symptoms were abdominal pain (62%), gastrointestinal bleeding (40%), and/or abdominal mass (38%). The primary site was stomach in 50%, small bowel in 30%, colorectum in 15%, and esophagus in 5%. Virtually all the sarcomas were leiomyosarcomas. Distribution was uniform among the three histologic grades; although 88% of Grade 1 tumors could be completely excised, only 35% of Grade 3 tumors could be completely resected. The 5-year survival rate was 75% for Grade 1 tumors, 16% for Grade 2 tumors, and 28% for Grade 3 tumors ($p = 0.0013$, Grade 1 *vs.* 2 and 3). Thirty of the 51 patients (59%) had curative resection with an operative morbidity rate of 24% and an operative mortality rate of 12%; at 5 years the disease-free survival rate was 58% and the overall survival rate was 63% (48% at 10 years). Eleven patients (42%) had recurrent disease develop at a median interval of 2 years after complete tumor excision. Twenty-one patients (41%) had partial excision or biopsy only of their tumors with an operative morbidity rate of 28%, operative mortality rate of 8%, and median survival of only 9 months. Overall, patients whose tumors were confined to the site of origin had a 58% 5-year survival rate compared with 20% for those whose tumors had invaded adjacent organs ($p < 0.05$). If the tumor was less than 10 cm in size, the 5-year survival rate was 78%, significantly better than the 38% for tumors greater than 10 cm ($p = 0.03$). These data suggest that histologic grade, local invasiveness, size, and extent of resection are the most important prognostic factors for patients with primary gastrointestinal sarcomas. Patients who have resection of all gross tumor, especially if it is well differentiated and localized, have a good prognosis.

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GASTROINTESTINAL SARCOMAS are uncommon tumors, constituting 1–2% of all gastrointestinal malignancies and about 10% of all sarcomas.[1,2] The literature consists mostly of isolated case reports, and only a few studies of gastric or intestinal leiomyosarcomas from any one institution are reported. There is wide variation in reported survival rates and no uniform therapeutic approach. However, in recent years there has been considerable progress made in the pathologic interpretation of soft tissue sarcomas in general, thus enabling a more accurate assessment of prognostic variables.

The purpose of this review is to analyze the management of primary gastrointestinal sarcomas at the Medical College of Virginia (MCV), to delineate their natural history, and to investigate the influence of various factors on prognosis.

Materials and Methods

Fifty-one patients were treated at MCV from 1952 to 1984 for primary gastrointestinal sarcomas. Pediatric rhabdomyosarcomas have been excluded from this study because of their different natural history since the advent of combined modality therapy.[3] Charts and histopathologic slides were reviewed to determine clinical presentation, histologic type and grade of the tumor, extent of surgical resection, operative morbidity and mortality rates, the use of radiation and/or chemotherapy in addition to surgery, pattern of recurrence and metastases, and survival data.

For the purpose of this review, resection was considered complete if all gross disease was removed and the microscopic margins were tumor-free. Partial resection included those cases in which the bulk of tumor was removed but gross or microscopic disease remained.

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TABLE 1. *Histopathologic Grading of Gastrointestinal Sarcomas*

Grade 1	Well differentiated Moderate cellularity Lack of anaplasia 0–4 mitoses/10 high-power fields
Grade 2	Moderately differentiated Moderate cellularity Mild anaplasia 5–9 mitoses/10 high-power fields
Grade 3	Poorly differentiated Marked cellularity Marked anaplasia ≥10 mitoses/10 high-power fields

Survival curves were plotted by use of Cox's proportional hazards model.[4]

The histologic slides were characterized in terms of differentiation, cellularity, anaplasia or atypia, and mitotic index. These tumors were then graded according to the criteria indicated in Table 1.

Results

Clinical Presentation

The mean age of the patients with gastrointestinal sarcomas was 53 years (range: 9–83 years). There was a slight male predominance, with a ratio of 1.8:1. The most common presenting complaint was abdominal pain, which was present in 62% of the patients. Forty per cent of the patients had evidence of gastrointestinal blood loss. Thirty-six per cent of patients had significant weight loss, and 28% complained of anorexia, nausea, or vomiting. The average duration of symptoms was 4.4 months (range: less than 1–24 months). An abdominal mass was palpable on physical examination in 38% of the patients (Table 2).

The average diameter of tumors was 11 cm (range: 1.5–23 cm). The tumors were slightly smaller in those patients having complete resection, but this was not statistically significant.

The distribution of the gastrointestinal sarcomas according to location is shown in Table 3. More than half of the tumors were located in the stomach, with 14 in the small intestine, eight in the colorectum, and only three in the esophagus.

TABLE 2. *Presenting Signs and Symptoms of Patients with Gastrointestinal Sarcomas*

Signs and Symptoms	No. of Patients	Percentage
Abdominal pain	31	62
Gastrointestinal bleeding	20	40
Abdominal mass	19	38
Weight loss	18	36
Anorexia, nausea, and vomiting	14	28

TABLE 3. *Distribution of Gastrointestinal Sarcomas*

Site	Number	Percentage
Esophagus	3	6
Stomach	26	51
Duodenum	3	6
Jejunum	7	13
Ileum	4	8
Colon	5	10
Rectum	3	6
Total	51	100

Histopathology

Virtually all the tumors were leiomyosarcomas, of which 44 were spindle cell type and five were epithelioid cell type (also known as malignant leiomyoblastoma). There was one malignant fibrous histiocytoma located at the base of the appendix and one hemangiopericytoma located in the sigmoid colon, representing extremely rare locations for these histologic types.

Table 4 shows the distribution of histologic grade in terms of those patients having complete *versus* partial resection of their tumors. Although there was a near uniform distribution of tumors between the three tumor grades, there was a marked difference in the extent of surgical resection possible among the three groups classified by grade. Almost all the patients with Grade 1 tumors could have complete resections, whereas only one-third of the Grade 3 tumors could be resected completely.

Extent of Surgery

Thirty of the 51 patients (59%) had complete resection of their tumors. These patients had 33 operations in which their tumors were completely excised; 27% of these operations necessitated resection of adjacent organs to ensure adequate margins. The most frequent adjacent organs resected were spleen and tail of pancreas (in association with gastric sarcomas); there was one pancreaticoduodenectomy plus nephrectomy performed to completely excise a sarcoma of the duodenum. There was a 24% incidence of postoperative complications in these patients, the most frequent being wound infections and sepsis. There were four deaths (12% operative mortality rate) among those patients having complete excision; three of those resulted from

TABLE 4. *Histologic Grade of Gastrointestinal Sarcomas*

	Grade 1	Grade 2	Grade 3
Complete excision	14	11	5
Partial excision	2	10	9
Total	16	21	14

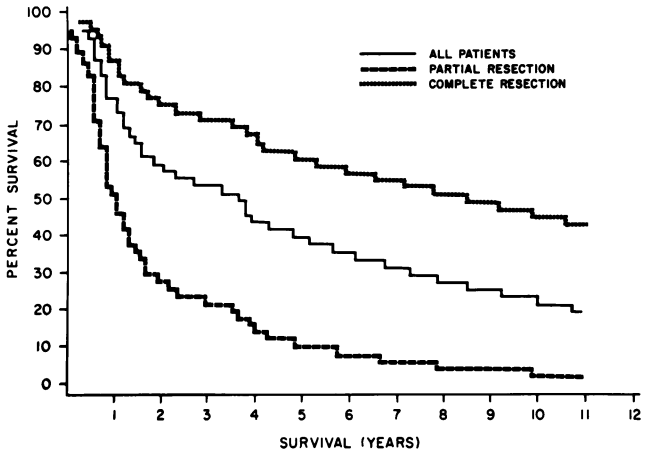

FIG. 1. Actuarial survival curves for patients having complete or partial resection of primary gastrointestinal sarcomas.

sepsis and occurred during the first 6 years of the review. The other death resulted from breakdown of the gastrojejunostomy and overwhelming sepsis in the patient who had a pancreaticoduodenectomy.

Twenty-one patients (41%) had 25 operations with partial excision or biopsy only of their tumors; the morbidity rate was 28% and operative mortality rate was 8% in this group of patients having palliative operations.

Pattern of Recurrence and Metastases

Twelve of the 26 patients (46%) who survived complete resection had recurrent disease develop. The recurrence was initially local in three patients; 10 of the 12 patients eventually had distant metastatic disease develop. The median interval from initial resection to detection of recurrence in these 12 patients was 2 years (range: 6–98 months). The three patients whose recurrence was local had complete excision of the recurrent tumor, with one patient surviving 16 years with no evidence of disease and the other two patients dying from recurrent tumor 12 and 31 months after re-excision.

Twenty-eight of the 51 patients (55%) had documented distant metastases or subsequently had them develop. The most common sites of metastases were liver (65%), peritoneum (43%), regional nodes (28%), and omentum (18%). There were only three cases of extra-abdominal metastases, and these were all located in the lung. Among all patients with gastrointestinal sarcomas, there was a 15% incidence of metastases to regional lymph nodes.

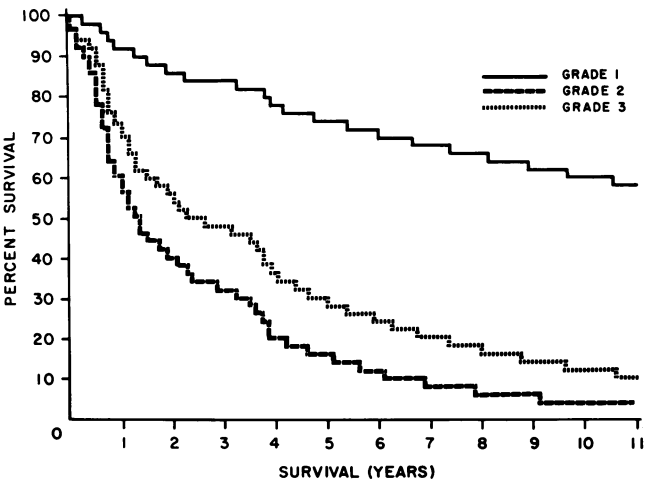

FIG. 2. Actuarial survival curves for all patients with primary gastrointestinal sarcomas based on grade of tumor.

Survival

The 5-year survival rate for all patients with gastrointestinal sarcomas treated at MCV during the period of study was 40%. When the data were analyzed according to the extent of resection, it is clear that complete excision afforded the only hope for long-term survival. The 5-year survival rate for patients who had complete resection was 63%, as compared with 10% surviving at 5 years after partial excision ($p < 0.0001$). At 10 years the overall survival rate for patients having complete tumor resection was 48% (Fig. 1). The 5-year disease-free survival rate of patients having complete resection was 58%.

Various prognostic factors were analyzed to determine their effect on survival. Analysis of survival data based on grade of tumor revealed a significantly better 5-year survival rate of 75% for patients with Grade 1 tumors, as compared with 16% and 28% for Grade 2 and 3 tumors, respectively ($p = 0.0013$); there was no significant difference between Grades 2 and 3. The 10-year survival rate for Grade 1 tumors was 60% but was less than 10% for Grades 2 and 3 (Fig. 2). Those patients with tumors smaller than 10 cm had a significantly better 5-year survival rate of 78% as compared with 38% for those patients whose tumors were greater than or equal to 10 cm ($p = 0.03$) (Fig. 3). There was also a significant improvement in the 5-year survival rate (58%) in those patients whose tumors were confined to the site of origin when compared with patients whose tumors invaded adjacent organs (20%) ($p = 0.05$). There were no 5-year survivors among those patients who had distant metastases, and their median survival was only 10 months (Fig. 4). There were no statistically significant differences in terms of survival between sarcomas located in the stomach, small bowel, or colorectum. Other factors, such as sex of the patient or duration of symptoms, also did not correlate with survival.

Radiation and/or Chemotherapy

Of the 21 patients who had partial resection of their tumors, 12 (57%) also received therapeutic radiation

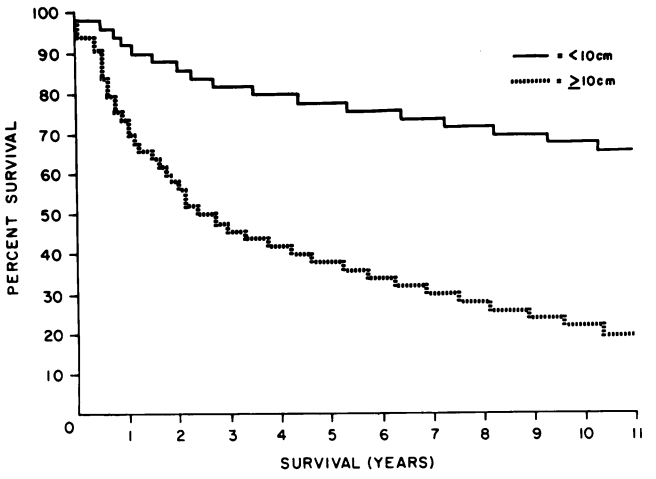

FIG. 3. Actuarial survival curves for all patients with primary gastrointestinal sarcomas based on size of the primary tumor.

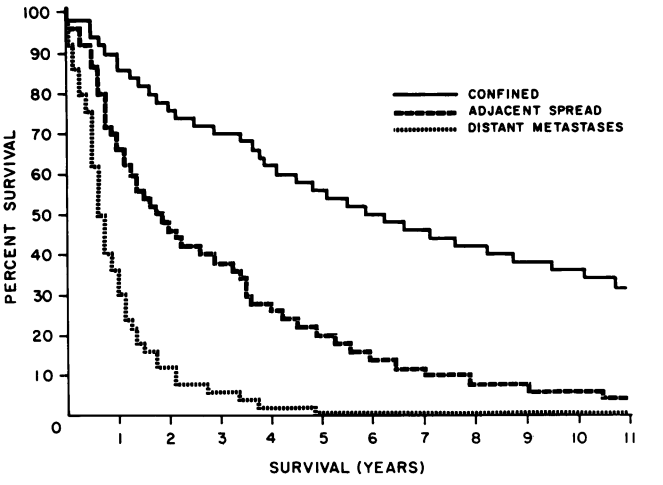

FIG. 4. Actuarial survival curves for all patients with primary gastrointestinal sarcomas based on extent of disease.

and/or chemotherapy; there was no difference in survival when compared with those patients who had operation alone (Table 5). The most frequently used chemotherapeutic regimen was doxorubicin HCl (Adriamycin®; Adria, Columbus, OH) and DTIC, alone or in combination with vincristine and cyclophosphamide. Total radiation doses ranged from 4500 to 5400 rads.

Discussion

Gastrointestinal sarcomas are uncommon malignant tumors that occur throughout the entire alimentary tract. The distribution of these tumors in our series is similar to the review of the 725 gastrointestinal leiomyosarcomas in the literature as of 1965, which reported the distribution as follows: esophagus 5%, stomach 47%, small bowel 35%, and colorectum 12%.[2] Because the alimentary tract has more smooth muscle than any other part of the body, it is not surprising that virtually all gastrointestinal sarcomas are leiomyosarcomas. The malignant fibrous histiocytoma of the appendix and the hemangiopericytoma of the colon in our series represent extremely rare cases.

The most frequent clinical presentations are abdominal pain, gastrointestinal bleeding, and/or an abdominal mass. Of note is that more than two-thirds of the patients that had gastrointestinal bleeding could have complete resection of their tumors, suggesting that small tumors causing early symptoms had a more favorable prognosis. In the past the diagnosis of gastrointestinal sarcomas was usually made at the time of a laparotomy, prompted by either radiologic studies with abnormal findings, intestinal obstruction, or gastrointestinal bleeding. With the advent of fiberoptic endoscopy, a tissue diagnosis may be made before operation for gastric and colorectal tumors, which could aid in pretreatment management decisions.

Surgical resection is the treatment of choice for gastrointestinal sarcomas, and appropriate surgical management requires every effort for complete excision of the tumor with an adequate margin of normal tissue. Resection of adjacent organs is often necessary to ensure complete excision. Several reviews have shown that small tumors (<5 cm) of the stomach can be adequately treated by wedge gastric resection with a generous margin of normal gastric wall.[5-7] Larger gastric sarcomas may require subtotal or total gastrectomy, and this should include omentectomy and resection of juxtagastric nodes. There is a discrepancy in the literature regarding the prevalance of nodal spread of gastrointestinal sarcomas, with some reports indicating little or no spread to regional lymph nodes[6-9] and others reporting a 10–15% incidence of nodal spread.[5,10-12] Our patients demonstrated a 15% incidence of spread to regional lymph nodes from all gastrointestinal sarcomas. The incidence of metastases to regional lymph nodes was only 6% for Grade 1 tumors as compared with 19% for Grade 2 tumors and 21% for Grade 3 tumors. Although it may not be necessary to include regional nodes in the resection of Grade 1 tumors, the grade of the tumor cannot be accurately assessed until the entire specimen is resected. Thus, because of this small but definite incidence of spread to regional nodes, and because including these nodes in the resection does not increase the morbidity

TABLE 5. *Results of Therapeutic Radiation (RT) or Chemotherapy (CT) on Survival of Patients with Gastrointestinal Sarcomas*

	Patients		Median Survival (Months)
	No.	(%)	
Partial resection	21		9
Surgery ± RT ± CT	12	(57)	9
Surgery alone	9	(43)	10

rate, we recommend a wide segmental resection with associated mesentery and/or omentum for all gastrointestinal sarcomas.

Reported survival data after operations for gastrointestinal sarcomas have been extremely variable, especially with respect to gastric sarcomas. The rates for curative resection for gastric sarcomas have ranged from 68 to 90%, with an overall 5-year survival rate between 19% and 56% and a 5-year survival rate after curative resection ranging from 32 to 63%.[6,7,10,13,14] Reports on sarcomas of the small and large intestine have been more consistent with 5-year survival figures of between 40% and 50% for all patients and those receiving complete excision.[9,15-17] This review reports a 5-year survival rate of 40% for all patients with gastrointestinal sarcomas and 63% for those able to have complete excision of their tumors. There was no significant difference in survival rate between sarcomas located in the stomach as compared with those in the small or large intestine.

Several prognostic factors were analyzed to determine their effect on survival, and the most significant factor affecting survival was the histologic grade of sarcoma. The method of grading sarcomas in this review was similar to that initially described for soft tissue sarcomas[18,19] and that recently reported for use with gastrointestinal sarcomas.[6,7,20] Grading was determined by a composite observation of the mitotic rate, degree of atypia or anaplasia, degree of cellularity, and degree of differentiation. The mitotic count appears to be the most objective and reproducible feature when determining the grade of malignancy; however, as noted by Appelman and Helwig, this needs to be related to the histologic appearance of the tumor.[5] More recently, Appelman has tended to downgrade the value of using mitotic counts in evaluating malignancy in stromal tumors of the gut. He found that the site of the primary tumor may be more valuable in tumor behavior prediction than a set number of mitotic counts.[21,22] Nevertheless, our results show that once the diagnosis of sarcoma is established, no difference in survival occurred on the basis of tumor location. This review clearly demonstrates that low-grade sarcomas (Grade 1) had a much better prognosis than higher grade sarcomas (Grades 2 and 3). This observation is related to the fact that nearly all (88%) Grade 1 sarcomas could be completely excised and, of those, only 14% eventually had metastases develop, whereas only 35% of Grade 3 sarcomas could be resected for cure and for half of those metastatic disease eventually developed. Other factors that were associated with a better prognosis were smaller tumors (<10 cm) and tumors confined to the site of origin, as noted in previous reports.[7,10,16]

Our study demonstrated no benefit from therapeutic radiation and/or chemotherapy; however, the number of patients treated was small and the role of radiation or chemotherapy cannot be adequately assessed with so few cases. Review of the literature has also failed to reveal a significant benefit from these nonsurgical modalities in an adjuvant or therapeutic setting.[6,7,15] However, the 42% recurrence rate in patients with curative resection in this review and reports that up to 78% of patients will eventually have distant metastases develop[5,6,20] warrant further investigation into the role of adjuvant therapy.

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